REMARKS/ARGUMENTS

The Applicants respectfully request reconsideration of the present application.

By the amendments, Applicants do not acquiesce to the propriety of any of the Examiner's rejections and do not disclaim any subject matter to which Applicants are entitled. *Cf. Warner Jenkinson Co. v. Hilton-Davis Chem. Co.*, 41 U.S.P.Q.2d 1865 (U.S. 1997).

In the Claims

Claims 33 and 35-45 remain under examination in this application. Claims 33 and 41 have been amended as discussed below.

No new matter has been added as a result of the claim amendments.

Claim Objections

Claim 41 has been amended to correct a grammatical error.

35 U.S.C. §112 Rejections

Claims 33 and 35-44 have been rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which application regards as the invention. Applicants have amended claim 33 to recite "providing pre-formed microparticles of the diketopiperazine derivative...." Applicants respectfully assert that the claim is now internally consistent and respectfully request withdrawal of the rejection of claims 33 and 35-44 on this basis.

35 U.S.C. §102 Rejections

Claims 33 and 35-36 have been rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Steiner et al. (WO 96/3614; hereinafter "Steiner"). It is the Office's position "that an ordinary skilled artisan could envisage the claimed method of instant claims 33 and 36 wherein the diketopiperazine microparticles are made from either 2,5-diketo-3,6-di(4-succinyl-aminobutyl)piperazine or alternatively, 2,5-diketo-3,6-di(4-fumaryl-aminobutyl)piperazine, the therapeutic agent is insulin, and the insulin is

inherently complexed to said microparticles." (Office Action dated March 23, 2009, hereinafter "OA", page 4). Applicants respectfully disagree.

A claim is anticipated under 35 U.S.C. §102 only if each and every element as set forth in a claim is found, either expressly or inherently described, in a single prior art reference (MPEP §2131; *Verdegaal Bros. V. Union Oil Co. of California*, 814 F.2d, 628, 631, 2 USPQ2d 1051 (Fed. Cir. 1987)). A claimed invention is anticipated only when it is "known to the art in the detail of the claim." *Karsten Manufacturing Corp. v. Cleveland Golf Co.*, 242 F.3d 1376, 1383 (Fed. Cir. 2001). In other words, not only must the limitations of the claim be shown in a single prior art reference, the limitations must be "arranged as in the claim." *Id.*

Claims 33, 35 and 36 are drawn to a method for delivering monomeric or dimeric insulin to a patient in need thereof, comprising administering to the patient a delivery formulation for the monomeric or dimeric insulin comprising an effective amount of insulin complexed with a diketopiperazine derivative, wherein the delivery formulation is prepared by complexing the insulin with microparticles of the diketopiperazine derivative.

Steiner discloses systems for pulmonary administration (page 3, line 27 to page 4, line 2). The system has microparticles having a diameter of between 0.5 and 10 microns (Id.). The microparticles are formed by co-precipitating a diketopiperazine derivative and a drug (page 2, lines 5-10 and page 4, line 23). There is no disclosure of a method for delivering insulin wherein the delivery formulation is prepared by complexing the insulin with microparticles of the diketopiperazine derivative and monomeric or dimeric insulin is released upon dissociation.

Nor does Steiner disclose the subject matter of claims 33, 35 and 36 under the principles of inherency. Under the principles of inherency, if the prior art necessarily functions in accordance with, or includes, the claimed limitation, it anticipates. *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 51 USPQ2d 1943 (Fed. Cir. 1999). Inherency may not be established by probabilities or possibilities. See *Scaltech Inc. v. Retec/Tetra.*

L.L.C., 178 F3d 1378, 51 USPQ2d 1055 (Fed. Cir. 1999). The mere fact that a certain thing may result from a given set of circumstances is not sufficient to establish inherency. *Id.* Where a reference provides a general disclosure such that one skilled in the art would not necessarily recognize that an element is disclosed in the reference, such a reference is not one that inherently anticipates the element. See, i.e., *Finnigan Corp. v. U.S. Int'l Trade Comm'n*, 180 F.3d 1354, 1365, 51 USPQ2d 1001, 1009 (Fed. Cir. 1999). In relying on the theory of inherency, the Office must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied reference. *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Int'f 1990).

Claims 33, 35 and 36 require that the diketopiperazine microparticle complex release monomeric or dimeric insulin as opposed to Steiner which teaches neither complexation nor non-hexameric insulin. .

The Office asserts that "the process described on pages 13-14 of Steiner inherently includes a suspension of diketopiperazine, because the solution described on page 13 is not described as being clear and thus could reasonably include suspended microparticles." OA, page 4. Applicants respectfully disagree with the Office's interpretation that the Steiner compositions inherently include the claimed microparticles. The process described on pages 13-14 of Steiner describes the pH-based precipitation of microparticles from a dissolved diketopiperazine. Whether or not "the solution … could reasonably include suspended microparticles" is not the standard of inherency. It is abundantly clear from the reference that it is not necessary that the solution include suspended microparticles and as such it is not inherent that it do so.

Moreover, Applicants have demonstrated the physical differences between the microparticles of the instant claims and the microparticles of Steiner in the declaration of Dr. Marshall Grant filed on October 9, 2007 in the instant application. The Grant declaration demonstrates that the microparticles of Steiner and the microparticles of the instant invention, as formed by the methods disclosed in each specification, are clearly different. A copy of the submitted declaration is attached hereto for the convenience of

the Office. The Declaration is evidence that the compositions resulting from the two disclosures (of Steiner and of the instant application) are different and thus that Steiner does not inherently disclose the methods and particles of the instant claims

Steiner certainly does not recognize the desirability of making and using a composition that releases monomeric or dimeric insulin and further fails to provide guidance for making such a composition. In contrast, Examples 1 and 2 as described on pages 18-20 of the instant specification provide detailed guidance for one of ordinary skill in the art to make and use a delivery formulation which releases monomeric and/or dimeric insulin

Accordingly, Steiner does not disclose each and every element of claims 33, 35 and 36 and therefore does not anticipate these claims under 35 U.S.C. §102(b). Applicants respectfully request withdrawal of the rejection on this basis.

35 U.S.C. §103 Rejections

Claims 37-44 have been rejected under 35 U.S.C. §103(a) as allegedly being unpatenable over Steiner et al. in view of Edelman (Abstract only of: Type II Diabetes Mellitus," Advances in Internal Medicine, 1998, 43, pp449-500, hereinafter "Edelman"). The Office asserts that "the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention." (OA, page 8) Applicants respectfully disagree.

To maintain a proper rejection under 35 U.S.C. §103, the Office must meet four conditions to establish a *prima facie* case of obviousness. First, the Office must show that the prior art suggested to those of ordinary skill in the art that they should make the claimed composition or device or carry out the claimed process. Second, the Office must show that the prior art would have provided one of ordinary skill in the art with a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be adequately founded in the prior art and not in an applicant's disclosure. Third, the prior art must teach or suggest all the claim limitations.

In re Vaeck, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Fourth, if an obviousness rejection is based on some combination of prior art references, the Office must show a suggestion, teaching, or motivation to combine the prior art references ("the TSM test"). *In re Dembiczak,* 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999). Following *KSR Int'l Co. v. Teleflex, Inc.*, this fourth prong of the *prima facie* obviousness analysis must not be applied in a rigid or formulaic way such that it becomes inconsistent with the more flexible approach of *Graham v. John Deere*, 383 U.S. 1, 17-18 (1966); 127 S. Ct. 1727 (2007). It must still be applied, however, as the TSM test captures the important insight that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *Id.* at 1741 (citing *United States v. Adams*, 383 U.S. 39, 50-52 (1966)).

Steiner teaches systems for pulmonary administration (page 3, line 27 to page 4, line 2). The system includes microparticles having a diameter of between 0.5 and 10 microns (Id.). The microparticles are formed by co-precipitating a diketopiperazine derivative and a drug (page 2, lines 5-10 and page 4, line 23). There is no teaching or suggestion of a method for delivering insulin wherein the delivery formulation is prepared by complexing the insulin with microparticles of the diketopiperazine derivative and monomeric or dimeric insulin is released upon dissociation.

Edelman does not cure the deficiencies of Steiner. Edelman teaches the use of combination therapy (bedtime intermediate-acting insulin in combination with daytime oral antidiabetic agents) for the treatment of Type II diabetes in obese patients. Edelman states that if the combination therapy is not successful, a split-mixed regiment using premixed 70/30 insulin pre-breakfast and pre-dinner can be used. Edelman contains no teaching or suggestion of diketopiperazine microparticles, let alone complexing insulin with diketopiperazine microparticles to form microparticles having a coating of insulin thereon. Furthermore, Edelman does not teach or suggest a delivery formulation that releases monomeric or dimeric insulin.

Regarding the Office's assertion that the microparticles of Steiner, formed by co-precipitation in bicarbonate, and those of the declaration submitted on October 9, 2007

(declaration of Dr. Marshall Grant) are different, Applicants respectfully disagree. The declaration of Dr. Grant was submitted solely for the purpose of demonstrating the differences between compositions formed by co-precipitation and those formed by complexation and that the insulin and DKP derivative in the particles formed by co-precipitation are not inherently complexed. Even if the particles prepared by the method of Experiment 1 of the Grant declaration (paragraph 8 of the declaration) were different than the Steiner particles, and Applicants respectfully assert that they are not different, co-precipitation experiments 2 and 2a (paragraphs 9 and 10 of the declaration) involved co-precipitation in sodium bicarbonate and therefore are substantially the same as the microparticles of Steiner. The microparticles of Steiner are co-precipitated while the claimed microparticles are complexed with the active agent and the microparticles formed by the two methods are not the same.

Therefore, because the combination of Steiner and Edelman do not teach or suggest all the limitations of claims 37-44, the Office has not established *prima facie* obviousness of these claims over Steiner in view of Edelman. Applicants respectfully request the withdrawal of the rejection on this basis.

Double Patenting

I. Claims 33 and 35-39 have been rejected on the grounds of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1, 4-7 and 10-14 of US Patent No. 6,071,497 (hereinafter "the '497 patent"). Applicants respectfully disagree.

The policy behind the judicially-created doctrine of obviousness-type double patenting is "to prevent the unjustified or improper timewise extension of the 'right to exclude' granted by a patent." However, the Applicants respectfully submit that allowance of the Applicants' pending claims 33 and 35-39 would clearly not lead to an improper timewise extension of the claims in the '497 patent.

The claims of the instant application are drawn to a method of treatment utilizing a delivery formulation for monomeric or dimeric insulin comprising particles formed by

complexing insulin to pre-formed microparticles of diketopiperazine according to a specified process.

The claims of the '497 patent are drawn to microparticulate systems and methods for delivery comprising microparticles incorporating therapeutic, prophylactic or diagnostic agents.

The Office asserts that although "the cited claims of USPN '497 do not recite that the insulin is complexed to the diketopiperazine, it would have been apparent that this associative interaction is a property of a composition comprising both a diketopiperazine and insulin." (OA, page 9) Applicants respectfully assert that there is no basis in fact for this statement. The microparticles of the instant claims and those of the '497 patent are made by different processes and have different properties as set forth in the declaration of Dr. Marshall Grant.

The processes of the '497 patent involve formation of diketopiperazine microparticles in the presence of the active agent by co-precipitation of the diketopiperazine and the active agent. In contrast, the microparticles of the instant claims comprise pre-formed diketopiperazine microparticles complexed with insulin such that the insulin forms a coating on the microparticle and which release monomeric or dimeric insulin upon dissociation. Complexation, and the formation of a coating of active agent on a diketopiperazine microparticle, is not an inherent property of a microparticle formed by the co-precipitation method of the '497 patent. The claims of the '497 patent do not require that the agent be complexed on the surface of the particle, as do the instant claims, and there is nothing that would make such a requirement obvious.

Furthermore, none of claims 1, 4-7 and 10-12 of the '497 patent require release of monomeric or dimeric insulin from the microparticles, as is required by the instant claims. The claimed invention is not obvious in view of the claims of the '497 patent. The claimed microparticles, have improved properties neither inherent to nor suggested by the Steiner microparticles as claimed, such as comprising a coating of insulin on the

microparticle surface (complexation), the ability to release monomeric or dimeric insulin, improved stability and consistent incorporation of insulin onto the microparticle. These are properties of the claimed microparticles that are not required by and are not obvious from the claims of the '497 patent. The subject matter of the instant claims is patentably distinct from that of the claims of the '497 patent. The claims of the '497 patent do not provide a teaching or suggestion to make or use the claimed microparticles having the disclosed properties. Therefore, one of ordinary skill in the art would not discern the method of instant claims 33 and 35-39 from claims 1, 4-7 and 10-14 of the '497 patent.

Thus, the methods recited in claims 33 and 35-39 of the instant application are patentably distinct from the methods and systems recited in claims 1, 4-7 and 10-14 of the '497 patent. Additionally, there is nothing in the art that teaches or suggests that the methods covered by the Applicants' claims are equivalent to the methods and systems covered by the claims of the '497 patent, which would allow the Applicants to make a claim that someone using the methods and systems covered by the '497 patent would necessarily be infringing the Applicants' claims. Moreover, the Applicants' claims are not just obvious variations of claims 1, 4-7 and 10-14 of the '497 patent that would extend the patent term of the '497 patent. Therefore, Applicants respectfully request the withdrawal of the double patenting rejection of instant claims 33 and 35-39 over claims 1, 4-7 and 10-14 of the '497 patent.

II. Claims 33 and 35-39 have been rejected on the grounds of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1, 4-7 and 10-14 of US Patent No. 6,248,771 (hereinafter "the '771 patent"). Applicants respectfully disagree.

The Applicants respectfully submit that allowance of the Applicants' pending claims 33 and 35-39 would clearly not lead to an improper timewise extension of the claims in the '771 patent.

The claims of the instant application are drawn to a method of treatment utilizing a delivery formulation for monomeric or dimeric insulin comprising particles formed by

complexing insulin to pre-formed microparticles of diketopiperazine according to a specified process.

Claims 1, 4-7 and 10-12 of the '771 patent are drawn to a microparticulate system for drug delivery to the pulmonary system and the method of using the system by administration to the lungs. The system has synthetic biodegradable microparticles of a diameter between 0.5 microns and 10 microns formed of a material which can be a diketopiperazine that releases an incorporated therapeutic, prophylactic, or diagnostic agent at a pH of 6.0 or greater, in a pharmaceutically acceptable carrier for administration to the lungs. The agent can be insulin and other therapeutic, prophylactic or diagnostic agents.

The Office asserts that although "the cited claims of USPN '771 do not recite that the insulin is complexed to the diketopiperazine, it would have been apparent that this associative interaction is a property of a composition comprising both a diketopiperazine and insulin." (OA, page 10) Applicants respectfully assert that there is no basis in fact for this statement. The microparticles of the instant claims and those of the '771 patent are made by different processes and have different properties as set forth in the declaration of Dr. Marshall Grant.

The processes of the '771 patent involve formation of diketopiperazine microparticles in the presence of the active agent by co-precipitation of the diketopiperazine and the active agent. In contrast, the microparticles of the instant claims comprise pre-formed diketopiperazine microparticles complexed with insulin such that the insulin forms a coating on the microparticle and which release monomeric or dimeric insulin upon dissociation. Complexation, and the formation of a coating of active agent on a diketopiperazine microparticle, is not required by the claims of the '771 patent. The claims of the '771 patent do not require that the agent be complexed on the surface of the particle, as do the instant claims, and there is nothing that would make such a requirement obvious.

Furthermore, none of claims 1, 4-7 and 10-12 of the '771 patent require release of monomeric or dimeric insulin from the microparticles, as is required by the instant claims. The claimed invention is not obvious in view of the claims of the '771 patent. The claimed microparticles, have improved properties neither inherent to nor suggested by the Steiner microparticles as claimed, such as comprising a coating of insulin on the microparticle surface (complexation), the ability to release monomeric or dimeric insulin, improved stability and consistent incorporation of insulin onto the microparticle. These are properties of the claimed microparticles that are not required by and are not obvious from the claims of the '771 patent. The subject matter of the instant claims is patentably distinct from that of the claims of the '771 patent. The claims of the '771 patent do not provide a teaching or suggestion to make or use the claimed microparticles having the disclosed properties. Therefore, one of ordinary skill in the art would not discern the method of instant claims 33 and 35-39 from claims 1, 4-7 and 10-14 of the '771 patent.

Thus, the methods recited in claims 33 and 35-39 of the instant application are patentably distinct from the methods and systems recited in claims 1, 4-7 and 10-14 of the '771 patent. Additionally, there is nothing in the art that teaches or suggests that the methods covered by the Applicants' claims are equivalent to the methods and systems covered by the claims of the '771 patent, which would allow the Applicants to make a claim that someone using the methods and systems covered by the '771 patent would necessarily be infringing the Applicants' claims. Moreover, the Applicants' claims are not just obvious variations of claims 1, 4-7 and 10-14 of the '771 patent that would extend the patent term of the '771 patent. Therefore, Applicants respectfully request the withdrawal of the double patenting rejection of instant claims 33 and 35-39 over claims 1, 4-7 and 10-14 of the '771 patent.

III. Claims 33, 35-39 and 42 have been provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 23-26 of co-pending US Patent Application No. 10/706,243 (hereinafter "the '243 application"). Applicants respectfully disagree.

The '243 application is a continuation of the '771 patent discussed *supra* and claims 23-26 are directed to a method for delivery of an active agent to the pulmonary system comprising administering to a patient in need of treatment an effective amount of microparticles which comprise a diketopiperazine and the active agent and which have a diameter between 0.5 microns and ten microns, in a pharmaceutically acceptable carrier for administration to the lungs, wherein the carrier is air, wherein the microparticles are administered from a dry powder inhaler or from a container for a dry powder inhaler; and wherein the active agent is released from the microparticle at a pH of 6.0 or greater. The claims of the '243 application do not require that the agent be complexed on the surface of the particle, as do the instant claims. Therefore, complexation, and the formation of a coating of active agent on a diketopiperazine microparticle, is not a required property of a microparticle formed by the co-precipitation method of the '243 application.

Furthermore, none of claims 23-26 of the '243 application require release of monomeric or dimeric insulin from the microparticles, as is required by the instant claims. The claimed invention is not obvious in view of the claims of the '243 application. The claimed microparticles, have improved properties neither inherent to nor suggested by the pending claims of the '243 application microparticles, such as comprising a coating of insulin on the microparticle surface (complexation), the ability to release monomeric or dimeric insulin, improved stability and consistent incorporation of insulin onto the microparticle. These are properties of the claimed microparticles that are not required by and are not obvious from the claims of the '243 application. The subject matter of the instant claims is patentably distinct from that of the claims of the '243 application. The claims of the '243 application do not provide a teaching or suggestion to make or use the claimed microparticles having the disclosed properties. Therefore, one of ordinary skill in the art would not discern the method of instant claims 33 and 35-39 from claims 23-26 of the '243 application.

Thus, the methods recited in claims 33, 35-39 and 42 of the instant application are patentably distinct from the methods and systems recited in claims 23-26 of the '243

application. Additionally, there is nothing in the art that teaches or suggests that the methods covered by the Applicants' claims are equivalent to the methods and systems covered by the claims of the '243 application, which would allow the Applicants to make a claim that someone using the methods and systems covered by the '243 application would necessarily be infringing the Applicants' claims. Moreover, the Applicants' claims are not just obvious variations of claims 23-26 of the '243 application that would extend the patent term of a patent issuing from the '243 application. Therefore, Applicants respectfully request the withdrawal of the provisional double patenting rejection of instant claims 33, 35-39 and 42 over claims 23-26 of the '243 application.

IV. Claims 33, 35 and 40 42 have been provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1-5 and 17-23 of co-pending US Patent Application No. 11/329,686.

The Office has instructed that a terminal disclaimer in compliance with 37 C.F.R. §1.321(c) or §1.321(d) may be used to overcome an actual or provisional rejection based on non-statutory double patenting ground. Without addressing the propriety of the Office's rejection, and specifically the Office's interpretation of what the cited references teach or suggest, Applicants respectfully and properly defer addressing the present rejection until there is otherwise allowable subject matter in at least one of the applications. Only then is it proper to assess the propriety of the Office's rejection in view of the potentially allowable claims. Accordingly, Applicants respectfully request reconsideration and withdrawal of the present rejections or that the rejections be held in abeyance until claims 33 and 35-44 are allowable in the present application, and claims are allowable in copending Application No. 11/329,686.

CONCLUSION

In light of the claim amendments and arguments presented *supra*, Applicants respectfully assert that the pending claims are in condition for allowance and request that a timely Notice of Allowance be issued in this case.

The Commissioner is authorized to charge any fee which may be required in connection with this Amendment to deposit account No. 50-3207.

Respectfully submitted,

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